Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors for Non–Small-Cell Lung Cancer Patients with Leptomeningeal Carcinomatosis

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Background: Leptomeningeal carcinomatosis (LC) is a detrimental complication of patients with non–small-cell lung cancer (NSCLC). The effect of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) on the clinical outcome of these patients, particularly those with *EGFR* mutations, has not been studied yet.

Methods: We searched the database for lung cancer patients diagnosed from 2003 to 2010 in one Asian medical center. NSCLC patients who also had LC diagnosed by either cytology or brain neuroimaging studies were identified. The treatments and clinical outcomes were reviewed.

Results: Of 5526 lung cancer patients, we identified 212 (3.8%) NSCLC patients with LC. Most patients (88.7%) had adenocarcinoma histology, and 129 (60.9%) patients had been treated with at least one regimen of EGFR TKI before the diagnosis of LC. One hundred and twenty-four (58.5%) patients were treated with EGFR TKI, and 128 (60.4%) patients were treated with whole-brain radiation therapy (WBRT) after the diagnosis of LC. The median overall survival was 4.5 months (95% confidence interval, 3.5–7.3). Multivariate analysis suggested that EGFR TKI therapy, WBRT, and cytotoxic chemotherapy were independent predictors for longer survival. Mutational status of *EGFR* was evaluated in 101 patients, and 75 mutations (74.3%) were detected. Among the 75 patients with *EGFR* mutations, EGFR TKI therapy and cytotoxic chemotherapy after diagnosis of LC remained the independent factors predictive of extended survival in the multivariate analysis.

Conclusions: Treatment of LC with EGFR TKI, cytotoxic chemotherapy, or WBRT in selected patients is associated with prolong survival period. These treatment options, especially EGFR TKIs, should be studied in patients with *EGFR* mutation-positive NSCLC and LC.

Key Words: Epidermal growth factor receptor tyrosine kinase inhibitor, Leptomeningeal carcinomatosis, Non–small-cell lung cancer, Prognosis, Whole-brain radiation therapy.

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Leptomeningeal carcinomatosis (LC) in patients with non–small-cell lung cancer (NSCLC) is not uncommon.[1] A previous report from our hospital revealed that the incidence of LC proven by cytology was 0.7% in all lung cancer patients (including those with small-cell lung cancer) from 1992 to 2002.[2] However, in our daily practice, most patients are diagnosed with LC through radiologic diagnosis, particularly magnetic resonance imaging (MRI), correlated to clinical symptoms such as headache and signs of increased intracranial pressure. As a consequence, the incidence is higher than previously reported. Given the improvement of systemic therapy for extracranial lesions of metastatic NSCLC, patients now live long enough to develop LC.[3] Whole-brain radiation therapy (WBRT) and intrathecal chemotherapy (ITC) were the only treatment choice before the emergence of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs).[4]

The development of EGFR TKIs, including gefitinib and erlotinib, has changed the treatment of patients with NSCLC in the past 10 years.[5–7] Patients whose tumors harbor activating *EGFR* mutations, such as deletions in exon 19 and exon 21 L858R mutation, respond more frequently to EGFR TKI therapy.[5,8–10] *EGFR* mutation status has been a predictor of improved survival in NSCLC patients with brain metastases, but its role in patients with LC is not clear.[11] Some authors have reported that EGFR TKIs were effective in treating LC in patients with *EGFR* mutations.[12–14] In several retrospective studies, EGFR TKI therapy for LC was found to prolong survival, but the impact of *EGFR* mutations was not clear because of the small number of patients who underwent EGFR gene testing.[15–20] Gefitinib and erlotinib were available

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commercially in Taiwan in 2003 and 2006, respectively, to treat metastatic lung cancer. In this study, we calculate the incidence of LC diagnosed by radiology and/or cytology/histology in the era of EGFR TKI therapy. We also analyze the survival of patients with LC who underwent various local or systemic treatments.

MATERIALS AND METHODS

We screened patients diagnosed with lung cancer at National Taiwan University Hospital from January 2003 to December 2010 by linking data from two institutional databases: the Cancer Registry and the Medical Coding Specialist Section of the Medical Information Management Office at National Taiwan University Hospital, Taipei, Taiwan. Patients with cytologically or histologically diagnosed NSCLC and LC diagnosed by either cerebrospinal fluid (CSF) cytology or neuroimaging were identified. Regarding neuroimaging, LC was defined as the presence of multifocal enhancing subarachnoid nodules on gadolinium-enhanced brain MRI or contrast-enhanced computed tomography (CT).

Medical records of these patients were reviewed. We evaluated the demographic data, histology type, *EGFR* mutation status, treatments before diagnosis of LC (including EGFR TKIs, WBRT, and surgical resection of preexisting brain metastases), initial presentation of LC, concurrent brain metastases status on diagnosis of LC, and the time from diagnosis of metastatic NSCLC by cytology/histology to the diagnosis of LC. Treatments after diagnosis of LC were recorded, including cytotoxic chemotherapy, EGFR TKIs, ITC, Ommaya reservoir implantation, and ventriculoperitoneal (VP) shunt operation. All these treatments were at the discretion of treating physicians. The protocol of this study was approved by the Institutional Review Board of National Taiwan University Hospital.

Statistical Analysis

Overall survival (OS) time was determined from the date of diagnosis of LC (date of CSF cytology or neuroimaging examination) to the date of death or last follow-up. Patients who were discharged against medical advice with the intention to die at home according to Chinese custom in the final stage of the dying process were recorded as a death event. Data were analyzed as a censor if a patient was unavailable to follow-up or survived beyond the final date of medical record access (December 31, 2011).

The OS was estimated by the Kaplan–Meier method, and the differences between the study groups were compared by the log-rank test. Cox's proportional hazard model was used to estimate the univariate or adjusted hazard ratios and associated 95% confidence intervals (CI) to detect differences of OS. Multivariate analyses were performed by using the Cox's proportional hazard model, adjusted for gender, age, smoking status, and previous EGFR TKI therapy status of patients. Subgroup analyses focused on (1) patients with *EGFR* mutations and (2) EGFR TKI–pretreated patients who received another EGFR TKI therapy for LC or rechallenge of the previous EGFR TKI for LC with an EGFR TKI free interval of at least 6 months. Two-sided p values less than or equal to 0.05 were considered statistically significant. All analyses were performed by SAS statistics software, Version 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Of the total of 5526 lung cancer patients screened, 212 (3.8%) patients with NSCLC and LC were identified. The median patient age was 56 years (range, 29–87 yr), 127 (59.9%) were female, 155 (73.1%) were never smokers, and 188 (88.7%) had adenocarcinoma histology. One hundred and twenty-nine (60.9%) patients had undergone EGFR TKI therapy before the diagnosis of LC. Most patients (47.6%) were diagnosed with LC by MRI and 19 (9.0%) patients were diagnosed with LC by a positive CSF cytology study (Table 1). The median time from diagnosis of metastatic disease to diagnosis of LC was 10.7 months (range, −1.5 to 55.5), and 48 (22.6%) patients had LC at initial diagnosis of metastatic NSCLC. Sixty-five (30.7%) patients had brain metastases on diagnosis of LC (Table 2). The most common symptoms on diagnosis were headache (49.0%), nausea/vomiting (41.5%), dizziness (24.1%), conscious change (21.7%), neurological deficit (17.9%), unsteady gait (14.2%), and seizure (8.0%). Fifteen (7.1%) patients were asymptomatic on diagnosis of LC.

Regarding local treatment for LC, 128 (60.4%) patients underwent WBRT, 23 (11.8%) patients underwent ITC, 31 (14.6%) patients underwent VP shunt operation, and 22 (10.4%) patients underwent Ommaya reservoir implantation. Regarding systemic therapy, 124 (58.5%) patients underwent EGFR TKI therapy, 22 (10.4%) patients underwent platinum-based cytotoxic chemotherapy, and 56 (26.4%) patients underwent nonplatinum-based cytotoxic chemotherapy after LC diagnosis (Table 2).

A total of 142 patients died, and 10 patients were still alive at the cut-off date. The median follow-up time was 2.5 months (range, 0–34.3), and the median survival was 4.5 months (95% CI, 3.5–7.3; Fig. 1). The median survival of different diagnostic modalities among CT, MRI, and CSF cytology were 6.5, 3.7, and 4.3 months, respectively ($p = 0.268$). Regarding systemic therapy, patients who received EGFR TKI therapy after LC diagnosis had longer OS than patients who did not (median 9.5 versus 1.7 months, $p < 0.001$; Fig. 2*A*). Patients who underwent cytotoxic chemotherapy also had longer OS (median, 10.2 versus 2.8 months, $p < 0.001$; Fig. 2*B*). As for local therapy, patients who underwent WBRT for LC survived longer (median, 8.4 versus 1.8 months, $p < 0.001$; Fig. 2*C*), but patients who underwent ITC (Fig. 2*D*), VP shunt operation, and Ommaya reservoir implantation did not. In a multivariate analysis adjusted for gender, age (≥70 or <70), smoking status, EGFR TKI naive or EGFR TKI pretreated, VP shunt operation, Ommaya reservoir implantation, EGFR TKI therapy after LC diagnosis, cytotoxic chemotherapy, and WBRT remained predictors of prolonged survival (Table 3).

One hundred and one patients had known *EGFR* mutation status, and 75 (74.3%) had *EGFR* mutations (common activating mutations of deletions in exon 19 and exon 21 L858R mutation were detected in 68 patients). Among

TABLE 1. Patient Characteristics

Variable		
Total		212 (100)
Gender, N (%)	Male	85 (40.1)
	Female	127 (59.9)
Age (yr)	Median (range)	56 (29–87)
Smoking, N (%)	Never smoker	155 (73.1)
Histology, N (%)	Adenocarcinoma	188 (88.7)
	Nonadenocarcinoma	24 (11.3)
Stage, N (%)	I + II	9 (4.3)
	IIIA	13 (6.1)
	IIIB	14 (6.6)
	IV	176 (83.0)
EGFR mutation, N (%)	Unknown	111 (53.3)
	Wild type	26 (12.3)
	19 deletion or L858R	68 (31.1)
	Other mutations[a]	7 (3.3)
Brain metastases before LC diagnosis, N (%)	Presence	89 (42.0)
Previous WBRT before LC diagnosis, N (%)	Presence	54 (25.5)
Previous operation for brain metastases, N (%)	Presence	10 (4.7)
Previous EGFR TKI therapy before LC diagnosis, N (%)	Presence	129 (60.9)

[a]Other mutations included three exon 20 insertion, two exon 21 L861Q mutation, one exon 18 G719A mutation, and one exon 21 K860E mutation.

EGFR, epidermal growth factor receptor; LC, leptomeningeal carcinomatosis; TKI, tyrosine kinase inhibitor.

TABLE 2. Clinical Presentation and Treatment of LC

Variable		
Time from diagnosis of metastatic lung cancer to LC (mo)	Median (range)	10.7 (-1.5 to 55.5)
Sequence of LC and metastatic lung cancer, N (%)	LC as initial presentation of lung cancer	48 (22.6)
Modality of LC diagnosis, N (%)	MRI	101 (47.6)
	CT	92 (43.4)
	CSF cytology	19 (9.0)
Concurrent brain metastases, N (%)	Presence	65 (30.7)
Local treatment for LC, N (%)	WBRT	128 (60.4)
	ITC	25 (11.8)
	VP shunt	31 (14.6)
	Ommaya reservoir	22 (10.4)
Systemic therapy for LC, N (%)	EGFR TKIs	124 (58.5)
	Platinum-based chemotherapy	22 (10.4)
	Nonplatinum-based chemotherapy	56 (26.4)
EGFR TKI therapy, N (%)	Gefitinib	64 (30.2)
	Erlotinib	68 (32.1)
	Afatinib	7 (3.3)

LC, leptomeningeal carcinomatosis; MRI, magnetic resonance image; CT, computed tomography; CSF, cerebrospinal fluid; WBRT, whole-brain radiation therapy; ITC, intrathecal chemotherapy; VP shunt, ventriculoperitoneal shunt; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

these patients, 52 (69.3%) patients underwent WBRT, 49 (65.3%) patients underwent EGFR TKI therapy, and 32 (42.7%) patients underwent cytotoxic chemotherapy. The median survival in patients who underwent EGFR TKI therapy for LC was longer than in patients who did not (median, 10.9 versus 2.3 months, $p < 0.001$; Fig. 3*A*). Patients who underwent cytotoxic chemotherapy also had longer OS (median, 13.3 versus 4.1 months, $p = 0.017$; Fig. 3*B*). The median survival in patients who underwent WBRT for LC was longer than in patients who did not (median, 10.9 versus 2.4 months, $p = 0.002$; Fig. 3*C*). In multivariate analysis, EGFR TKI therapy and cytotoxic chemotherapy remained the predictors of prolonged survival (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/JTO/A893).

In a subgroup of EGFR TKI–pretreated patients in whom LC developed and who underwent another EGFR TKI therapy (n = 28) or rechallenge of previous EGFR TKI therapy, with an EGFR TKI free interval of at least 6 months (n = 6), 30 (88.2%) patients underwent gefitinib as EGFR TKI therapy before diagnosis of LC. Among these patients, 21 (61.8%) patients underwent WBRT, and 31 (91.2%) patients underwent erlotinib therapy for LC. The median treatment duration was 2.0 months (range, 0.1–15.6). Clinical response was recorded in 22 (64.7%) patients. The median survival of these patients was 9.5 months (95% CI, 4.4–13.3; Supplemental Fig. 1, Supplemental Digital Content 2, http://links.lww.com/JTO/A894).

DISCUSSION

In this current single institutional study, we demonstrated that the incidence of LC in NSCLC patients between 2003 and 2010 was 3.8% among all registered lung cancer patients. The incidence of LC in patients with *EGFR* mutation-positive or *EGFR* wild-type NSCLC was not calculated here because not all patients had known *EGFR* mutation status. The time from diagnosis of metastatic disease to diagnosis of LC was widely distributed. Some patients developed LC upon the diagnosis of metastatic disease, and some patients developed LC late after a long period of EGFR TKI therapy. This indicated that the biology of the tumors was different. The standard of diagnosis of LC is the presence of malignant cells in a CSF specimen. Gadolinium-enhanced MRI is the preferred choice of neuroimaging study to diagnose LC, and contrast-enhanced CT is the alternative choice, despite its lower sensitivity and specificity.[21] Many patients with LC cannot cooperate with lumbar puncture for CSF study or with a time-consuming MRI study because of neurologic symptoms, change in consciousness, or seizures. Contrast-enhanced CT could be a rapid diagnostic tool for these patients. In this study, 92 patients were diagnosed with LC by a contrast-enhanced CT. Among these patients, 33 (35.9%) patients had concomitant CSF study or MRI study to confirm the diagnosis of LC. We included all these acceptable diagnostic tools to minimize the bias of patient selection and to reflect our daily practice.

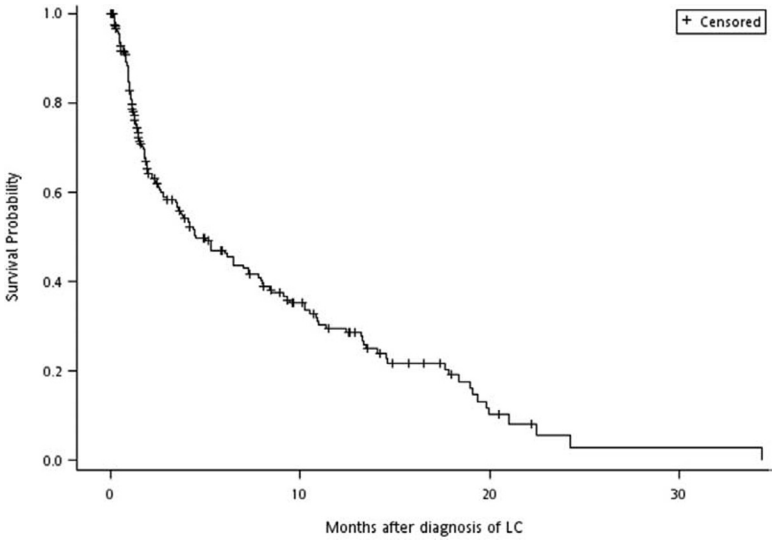

FIGURE 1. Overall survival of all patients from diagnosis of leptomeningeal carcinomatosis to death.

The median survival of this study cohort was 4.5 months. In other single institutional studies of the era of EGFR TKI therapy, the median survival ranged from 3.0 to 6.0 months in the overall study populations.[15–20] There was a trend toward a longer survival in patients who were diagnosed with LC by CT in this study. In our hospital, physicians use CT to follow-up patients with metastatic NSCLC, and many patients were diagnosed with LC by contras-enhanced CT early, while he or she was asymptomatic or having minimal symptoms. The survival was thus longer than previously reported. There was no difference in survival with respect to age. One reason is that only 31 patients were older than 70 years, and the number was relatively small. Another reason is that in patients with LC, performance status was a better predictor of survival than age as mentioned in another study.[17] The role of various local treatments for LC and their contribution to OS are controversial. Some authors have demonstrated that WBRT for LC is a predictor of better survival, but other authors have not.[15–17,19,20] The role of ITC is controversial as well.[17,19,20,22] In this study, 60.4% and 11.8% of patients underwent WBRT and ITC for

TABLE 3. Univariate and Multivariate Analysis for Survival in Overall Population

	Univariate		Multivariate	
Variables	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
Age				
<70	1.0			
≥70	1.40 (0.89–2.21)	0.150		
Sex				
Female	1.0		1.0	
Male	1.57 (1.12–2.20)	0.008	1.28 (0.82–1.98)	0.276
Smoking				
Never smoker	1.0		1.0	
Current or former smoker	1.53 (1.07–2.20)	0.021	1.19 (0.75–1.87)	0.466
EGFR TKI therapy before LC				
No	1.0		1.0	
Yes	1.63 (1.14–2.34)	0.007	1.23 (0.84–1.79)	0.287
Treatment for LC				
EGFR TKI	0.34 (0.24–0.48)	<0.001	0.33 (0.23–0.47)	<0.001
WBRT	0.38 (0.27–0.54)	<0.001	0.39 (0.27–0.56)	<0.001
ITC	0.90 (0.54–1.48)	0.667		
Chemotherapy	0.55 (0.39–0.78)	<0.001	0.53 (0.36–0.77)	<0.001
VP shunt operation	0.64 (0.40–1.02)	0.059		
Ommaya reservoir	0.94 (0.56–1.59)	0.811		

HR, hazard ratio; CI, confidence interval; LC, leptomeningeal carcinomatosis; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; WBRT, whole-brain radiation therapy; ITC, intrathecal chemotherapy; VP shunt, ventriculoperitoneal shunt.

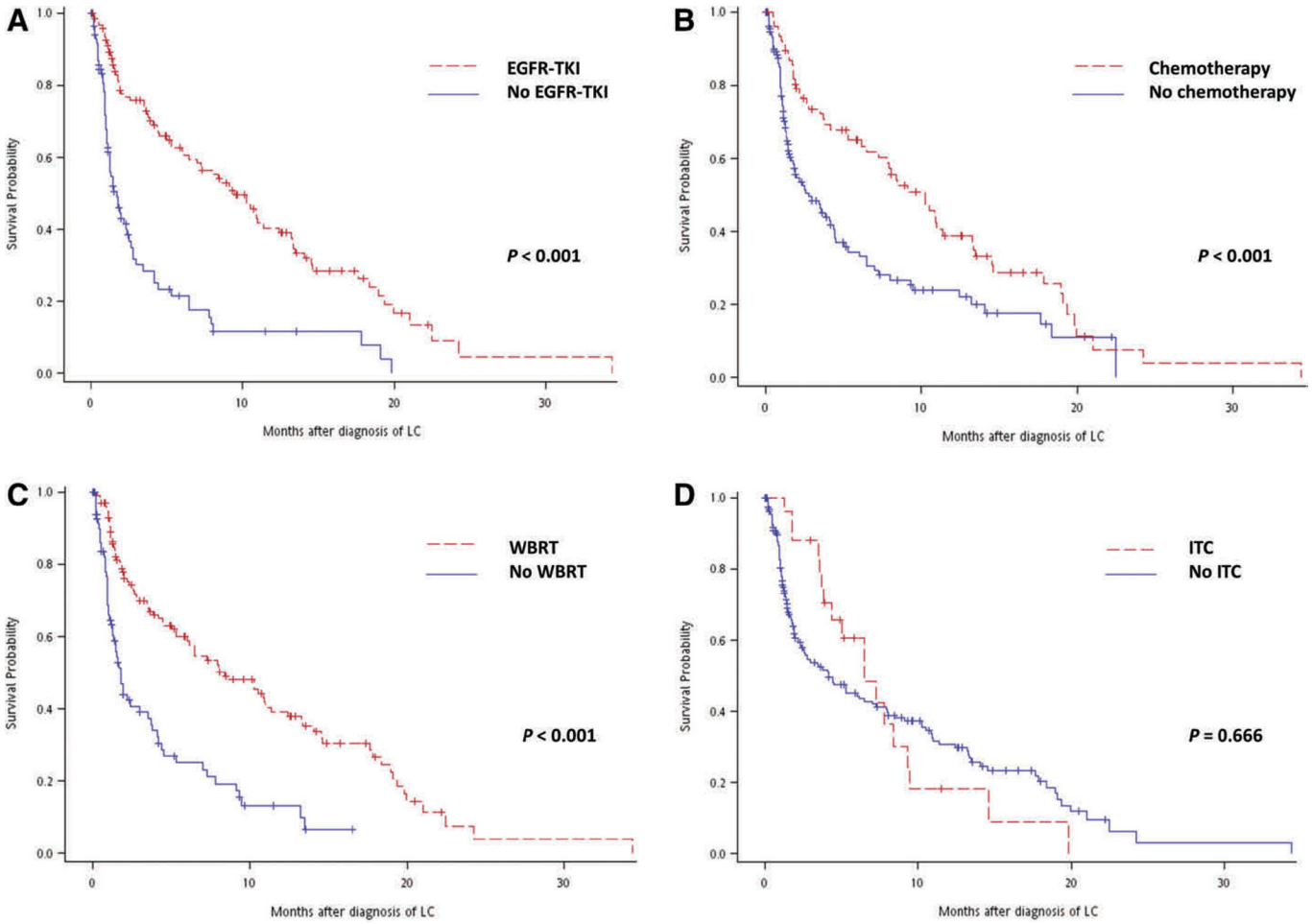

FIGURE 2. Kaplan–Meier analysis showing overall survival of all patients who (*A*) received (red) or did not receive (blue) epidermal growth factor receptor tyrosine kinase inhibitor therapy after diagnosis of leptomeningeal carcinomatosis (LC); (*B*) received (red) or did not receive (blue) cytotoxic chemotherapy after diagnosis of LC; (*C*) received (red) or did not receive (blue) whole-brain radiation therapy after diagnosis of LC; (*D*) received (red) or did not receive (blue) intrathecal chemotherapy after diagnosis of LC.

LC, respectively, and we demonstrated that WBRT was an independent predictor of prolonged survival, but ITC was not. The treatment protocol of ITC, however, was not unified in our hospital.

Regarding systemic therapy for LC, in case reports of various clinical scenarios, gefitinib and erlotinib have been proposed as effective treatments for LC.[14,23–27] Erlotinib was found to achieve a higher CSF concentration, and some physicians administered high-dose erlotinib to treat LC.[28–32] In these retrospective studies, EGFR TKI therapy conferred a survival benefit. Because only a few patients underwent *EGFR* gene testing, the survival benefit of EGFR TKI therapy for patients with *EGFR* mutations, however, is not clear. In this study, EGFR TKI therapy prolonged survival in patients whether or not they had EGFR TKI therapy before the diagnosis of LC. In patients with *EGFR* mutations, those who underwent EGFR TKI therapy had a significantly longer survival time, with a median survival of 10.9 months. To the best of our knowledge, this was the largest cohort of LC patients with a known *EGFR* mutation status. As for systemic cytotoxic chemotherapy, the impact on survival benefit is debatable.[16,17,19,20] In our series, patients who underwent cytotoxic chemotherapy for LC had longer survival both in the overall population and in the subgroup of patients with *EGFR* mutations. In Taiwan and East Asia, the prevalence of *EGFR* mutation-positive NSCLC is higher than in Western countries.[5,6] In the era of EGFR TKI therapy, patients with *EGFR* mutations underwent standard first-line treatment with an EGFR TKI, such as gefitinib, erlotinib, or afatinib.[33–38] A retrospective study revealed that the incidence of central nervous system (CNS) recurrence increased after an initial response to gefitinib.[3] In this study, most patients were diagnosed with LC after a median period of 10.7 months of treatment for metastatic lung cancer, and most of these patients had undergone prior EGFR TKI therapy. Takenaka et al.[23] report on a patient on gefitinib therapy in whom LC developed but who responded to erlotinib therapy. A retrospective study compared the efficacies of EGFR TKIs for treating LC, and erlotinib was shown to have a better control rate (64.3%, defined as cytologic negative conversion) of LC than did gefitinib.[39] *EGFR* T790M resistance mutation is the

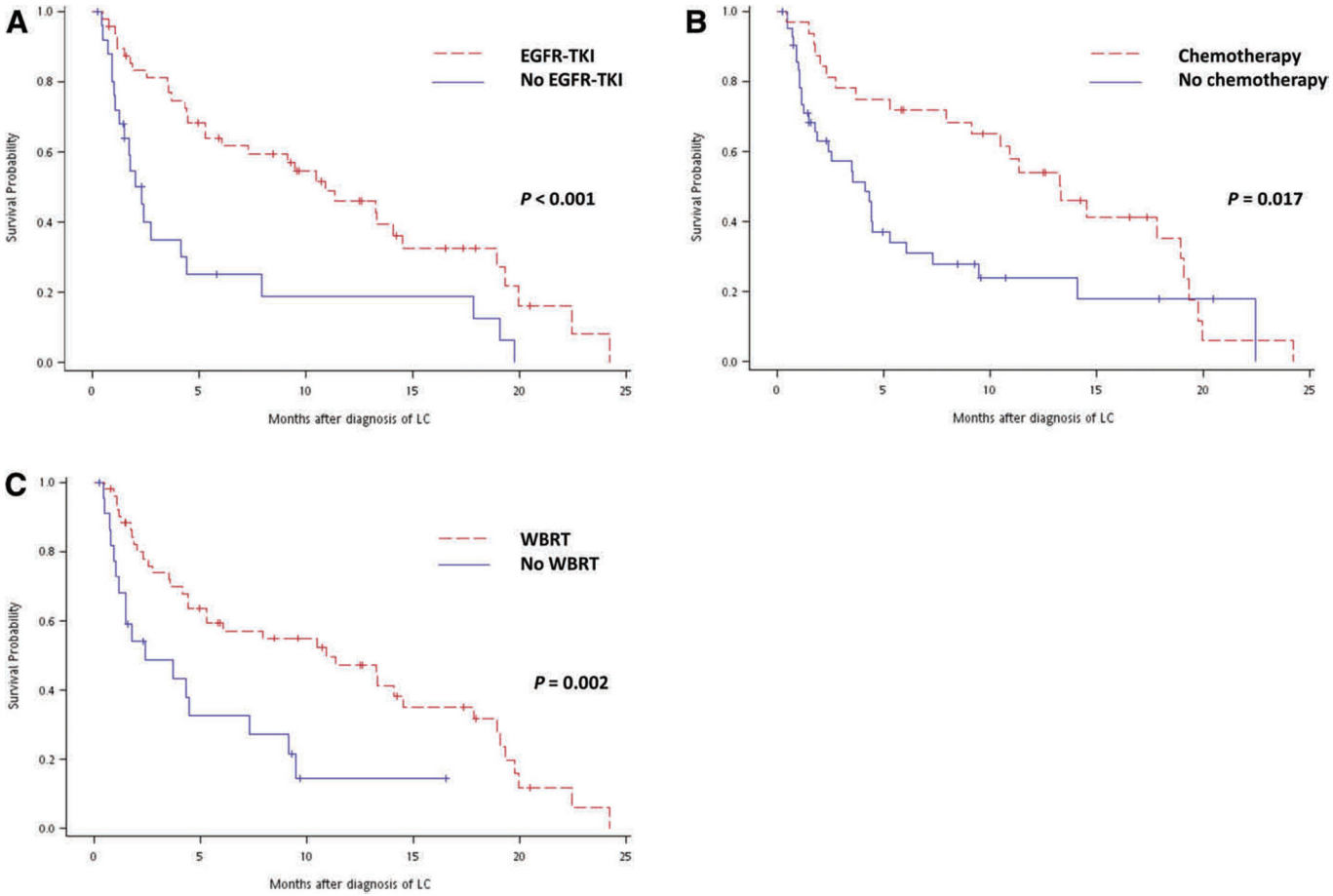

FIGURE 3. Kaplan–Meier analysis showing overall survival of patients with *epidermal growth factor receptor* (*EGFR*) mutations who (*A*) received (red) or did not receive (blue) EGFR tyrosine kinase inhibitor therapy after diagnosis of leptomeningeal carcinomatosis; (*B*) received (red) or did not receive (blue) cytotoxic chemotherapy after diagnosis of LC; (*C*) received (red) or did not receive (blue) whole-brain radiation therapy after diagnosis of leptomeningeal carcinomatosis.

main mechanism of acquired resistance to EGFR TKI therapy, which accounts for 60% of the patients who develop acquired resistance to EGFR TKI therapy.[40,41] However, a retrospective study revealed that in patients in whom acquired resistance to prior EGFR TKI therapy developed, acquired *EGFR* T790M resistance mutation was detected in only 1 out of 20 CSF specimens (5%).[42] In this study, we identified 34 patients who had undergone EGFR TKI therapy for metastatic disease before the diagnosis of LC who subsequently underwent another EGFR TKI therapy or rechallenge of a previous therapy, with an intervening period of at least 6 months, after the diagnosis of LC. Most patients in this subgroup were gefitinib pretreated and underwent erlotinib therapy for LC. The median survival was 9.5 months. This result implies that physicians should not exclude patients pretreated with an EGFR TKI from another EGFR TKI therapy or a rechallenge therapy after diagnosis with LC.

This retrospective study had several limitations. There were many censors in the survival curve. Among these patients, 60 patients did not return to our hospital after the last day of follow-up. Because our hospital is a tertiary referral medical center, many patients died at other hospitals and did not have formal records of death. The censors were randomly distributed and did not influence the results. The performance status was not recorded in this study, which was regarded as a good prognostic factor.[17] However, in a retrospective study, EGFR TKI therapy was still an independent good prognostic factor regardless of performance status.[17] In patients with certain clinical features or whose tumors harbor activating *EGFR* mutations, EGFR TKI therapy may provide a clinical benefit in patients with poor performance status.[43,44] Physicians should not exclude patients from EGFR TKI therapy according to performance status alone. The treatment modalities and the sequence of treatment for LC were heterogeneous, and we identified prognostic factors only by the presence of specific treatment. The synergistic effects of different treatments cannot be evaluated here.[45] Responses to various treatment modalities and the durations of response were difficult to evaluate, and it was difficult to attribute tumor response to one treatment modality while a patient was undergoing two or more treatment modalities. Patients may survive longer because of effective control of extracranial disease with EGFR TKI therapy or cytotoxic chemotherapy and effective control of brain metastases with WBRT. The true effects of

EGFR TKI therapy, cytotoxic chemotherapy, and WBRT on LC control cannot be concluded here. We used OS to measure the clinical benefits, which might not truly represent the tumor response. Other potential predictors of better survival outcome, such as CSF protein and white blood cell counts, were not evaluated in this study because only 9% of the study population underwent initial CSF study.[17]

The novel EGFR TKI afatinib was approved by regulatory authorities in 2013, and its effectiveness in treating CNS metastases (brain metastases and LC) has been suggested in a retrospective study.[46] In a case report, afatinib in combination with cetuximab was effective in treating LC.[47] In addition, novel EGFR TKIs designed to overcome acquired *EGFR* T790M resistance mutation, such as AZD9291 and rociletinib (CO-1686), are under clinical development, and activities against CNS metastases have been reported.[48–50] These novel agents and combination therapy may be effective in treating LC in the future.

In conclusion, in the era of EGFR TKI therapy, treatment of patients with LC using EGFR TKI, cytotoxic chemotherapy, and WBRT has been shown to prolong survival. Prospective study is still warranted to evaluate the impacts of novel EGFR TKIs, such as afatinib, AZD9291, and rociletinib on survival outcomes, especially for patients whose tumors harbor *EGFR* mutations.

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